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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/092,083	03/06/2002	David McCallister	214240	8537

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KATTEN MUCHIN ROSENMAN LLP
525 WEST MONROE STREET
CHICAGO, IL 60661-3693

EXAMINER	
JIANG, SHAOJIA A	

ART UNIT	PAPER NUMBER
1617	

DATE MAILED: 07/29/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/092,083	MCCALLISTER ET AL.	
	Examiner	Art Unit	
	Shaojia A. Jiang	1617	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *29 April 2005 and 23 September 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *44-52* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *44-52* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on April 29, 2005 has been entered.

This Office Action is in response to Applicant's request for continued examination (RCE) filed April 29, 2005, and amendment and response to the Final Office Action (mailed April 30, 2004), filed September 23, 2004 wherein claims 44-52 have been amended. Claims 1-31 and 32-43 are cancelled previously.

Currently, claims 44-52 as amended now are pending in this application and under examination on the merits.

Applicant's amendment filed September 23, 2004 with respect to the rejection of claims 44-52 made under 35 U.S.C. 112 first paragraph for containing new subject matter which was not described in the original specification and claims of record stated in the Office Action dated April 30, 2004 have been fully considered and found persuasive to remove the rejection since the new matter has been removed from the claims. Therefore, the said rejection is withdrawn.

Applicant's amendment which amends claim 48 with respect to the objection of record stated in the Office Action dated April 30, 2004 has been fully considered and is found persuasive. Therefore, the objection is withdrawn as to claim 48 only.

Claim Objection

Claims 49-50 objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the base claim 44 down to composition "consisting essentially of" recited ingredients. The composition of the base claim is actives recited therein. However, the transitional phrase, "contains", employed in the dependent claim 49 is synonymous with "comprising", "including," or "characterized by," which is inclusive or open-ended and does not exclude additional, unrecited elements or method steps. See, e.g., Genentech, Inc. v. Chiron Corp., 112 F.3d 495, 501, 42 USPQ2d 1608, 1613 (Fed. Cir. 1997). See also MPEP 2111.03. The addition of further actives in dependent claims is **broader** than the scope of the base claim and therefore improper. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. Additionally, claim 44 has recited "a solubilizing agent" already.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 49-50 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 49 recites "sweetener". There is insufficient antecedent basis for this limitation, the ranges of ingredients, in the claim since the independent claim 44 which claim 49 is dependent from does not recite any sweetener.

Moreover, the transitional phrases "consisting essentially of" already recited in the base claim 44. Thus, the open transitional phrases, "contains" in dependent claims herein are improper.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 44-52 are rejected under 35 U.S.C. 103(a) as being unpatentable over Katdare et al. (5,853,759, of record).

Katdare et al. discloses that bisphosphonates including instant preferred bisphosphonates such as alendronate are known to have utility as pharmaceutical agents for inhibiting bone resorption (see col.1 lines 14-42). Katdare et al. particularly discloses that a composition be administered orally comprising the instant preferred bisphosphonate, alendronate, is known to be useful in a method of treating osteoporosis

in postmenopausal women (human mammals) (see col.1 lines 43-49). The disclosed pharmaceutical effervescent formulations of alendronate therein in tablet and powders which are placed in an convenient amount of water to produce effervescent liquid (solution), and that the patient drinks the effervescent solution, are for eliminating or minimizing side effects during the medication (i.e., for treating osteoporosis and/or inhibiting bone resorption in a mammal) (see col.1 lines 8-11 and 48-57, col.2 lines 63-67). The particular disclosed alendronate effervescent compositions of Katdare et al. in Example 1-4 comprises alendronate in an effective amount (known for treating osteoporosis and/or inhibiting bone resorption), the instant preferred acid component, citric acid, and the instant preferred alkaline effervescing component, sodium bicarbonate and sodium carbonate, flavoring agent or sweetener and color agent, and then an convenient amount of water added to produce effervescent solution to be administered orally (see Example 1 at col.4 line 34-35 and 46-56 in particular), and the composition also comprises a lubricant such as sodium benzonate and polyethylene glycol (PEG) (also known as a solubilizing agent) (see col.2 lines 24-26 and col.4 lines 21-33).

Note that the total weight of the solid composition of Katdare et al. in claims 4-5 therein is 3.365 g, very close to 3.5 g as instantly claimed (see claims 4-5, adding up the weight of all solid ingredients); Moreover, the total weight of the table is known to range from about 100 to about 50,000 mg, about 1500-32500 mg, or about 20,800-30,150 mg (see col.3 lines 1-5).

The weight percentage of the acid component in Example 1 is 58.7 wt % (which is calculated by 650 mg of citric acid per 1106.5 mg of total weight, see Example 1 at col.4), which is substantially close to about 51-52 wt %, the instant claimed range; the weight percentage of the alkaline component in Example 1 is 36.8 wt % (which is calculated by 367+40 mg of sodium bicarbonate and sodium carbonate, per 1106.5 mg of total weight, see Example 1 at col.4), within the instant claimed range, 34-38 wt %. The amount of bisphosphonate such as alendronate in the prior art composition ranges from 1 to 80 mg, overlapping with the instant claim.

Regarding the inherent property, the pH of the solution, it is noted that citric acid is employed in an excess in the composition therein to efficiently generate the effervescence and to sequester any ions to complex with alendronate, and to enhance favor as well, disclosed by Katdare et al. (see col.3 lines 60-65). Thus, the solution therein is acidic. The pKa of citric acid (known to used as a buffer), pK_1, K_2, K_3 are 3.128, 4.761, and 6.396, respectively (provided by Bull "An Introduction to Physical Biochemistry" page 103, PTO-892). Thus, one of ordinary skill in the art would clearly recognize that the pH values in citric acid buffered solutions would be within the instantly claimed range about 4.5 to about 5.5, as shown in the calculation below:

Example I discloses that citric acid is 650 mg and the molecular weight (or formula weight, FW) of citric acid is 192.12 (provided by Aldrich Handbook page 436, PTO-892). Thus, the moles of citric acid is 650 ÷ 192.12 =3.38 mmol.

Example I discloses that sodium bicarbonate is 367 mg and the molecular weight of sodium bicarbonate is 84.01 (provided by Aldrich Handbook page 1505, PTO-892). Thus, the moles of sodium bicarbonate is 367 ÷ 84.01= 4.37 mmol.

Example I discloses that sodium carbonate is 40 mg and the molecular weight of sodium carbonate is 105.99 (provided Aldrich Handbook page 1498, PTO-892). Thus, the moles of sodium carbonate is 40 ÷ 105.99 =0.38 mmol.

It is known in the basic chemistry that the mole ratio of citric acid to sodium carbonate for neutralizing citric acid by sodium carbonate (or known as equal equivalent) is 2:3 (see col.3 line 67 to col.4 line 1) and the mole ratio of citric acid to sodium bicarbonate for neutralizing citric acid by sodium bicarbonate is 1:3.

Thus, 4.37 mmol of sodium bicarbonate neutralizes 4.37 X 1/3 = 1.46 mmol of citric acid;

2.65 mmol of sodium carbonate neutralizes 0.38 X 2/3 = 0.25 mmol of citric acid;

Therefore, the left or excess of citric acid in the solution

= 3.38 – (1.46 +0.25) =1.67 mmol.

Therefore, 1.67 mmol, about a half amount of citric acid is free and left in the solution. Thus, the solution is acidic. As discussed above, according the known pKa values of citric acid, the pH value of the effervescent composition of Example 1 could be within the instant claim.

Moreover, after administering of the effervescent solution of Katdare et al., the pH of the mammal's stormach would be inherently raised to the range here since the

citric acid solution is a known buffered solution which would mediate the pH in the mammal's stomach for a period of time.

Thus, oral administration of Kuznicki's effervescent composition to a mammal is useful in methods of treating osteoporosis and inhibiting bone resorption.

Katdare et al. does not expressly disclose that the total weigh of the solid compositions of the prior art is **about** 4.3 to about 6 grams such as 5000 mg (4.350 or 5 grams). Katdare et al. does not expressly disclose that the acid component is about 51-52 wt % by weight of solid compositions of the prior art.

It would have been obvious to a person of ordinary skill in the art at the time the invention was made to determine or optimize the total weigh of the solid compositions of the prior art to **about** 4.3 to about 6 grams such as 4.350 or 5 g, and the acid component to about 51-52% by weight of solid compositions.

One having ordinary skill in the art at the time the invention was made would have been motivated to determine or optimize the total weigh of the solid compositions of the prior art to about 4.3 to about 6 grams, since the claimed range 4.3 to about 6 grams lies inside ranges disclosed by the prior art, about 100 to about 50,000 mg, about 1500-32500 mg, or about 20,800-30,150 mg. Thus, a *prima facie* case of obviousness exists. See *In re Wertheim*, 541 F.2d 257, 191 USPQ 90 (CCPA 1976); In re Woodruff, 919 F.2d 1575, 16 USPQ2d 1934 (Fed. Cir. 1990). See also MPEP 2144.05.

Additionally, one having ordinary skill in the art at the time the invention was made would have been motivated to adjust the acid component to about 51-52% by weight of solid compositions since the weight percentage of the acid component

disclosed by Katdare et al. in Example 1 is 58.7 wt % is substantially close to about 51-52 wt %, the instant claimed range. Moreover, the determination or optimization of amounts of a known acid compound to be used to adjust the known pH of the buffering composition based on the prior art teachings, is considered well within conventional skills in pharmaceutical science, involving merely routine skill in the art.

It has been held that it is within the skill in the art to select optimal parameters, such as amounts of ingredients, in a composition in order to achieve a beneficial effect. See *In re Boesch*, 205 USPQ 215 (CCPA 1980).

Thus the claimed invention as a whole is clearly prima facie obvious over the teachings of the prior art.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 44-52 are rejected under 35 U.S.C. 103(a) as being unpatentable over Daifotis et al. (5,994,329, of record).

Daifotis et al. discloses the compositions of a bisphosphonate comprising a bisphosphonate including instant preferred bisphosphonates such as alendronate, in oral forms therein such as in effervescent compositions, and also comprising

solubilizing agents such as polyvivylpyrrolidone, coloring agents, and sweeteners (see col.1 lines 15-58, col.11 line 55 to col.12 lines 3, col.12 lines 3-34), especially the liquid formulation or composition of Example 8 employed in the methods of treatments herein in Examples 2-6 comprising alendronate salt in the amounts within the instant claim (see col.5 lines 44-45, Example 8 at col.19), the instant preferred acid component, citric acidand sodium citrate, and the alkaline component sodium hydroxide which is used to adjust the pH of the solution formulation to 6.75 (reads on the instant claim, about 6.5)(see particular Example 8 at col. 19 lines 40-62,). These compositions of a bisphosphonate be administered orally are useful for methods of treating osteoporosis and bone resorption in human mammals such as postmenopausal women (see also abstract, col.5 lines 21-23 and 29-35, col.7 lines 31-37, and Examples 2-6 at col.17-18).

Daifotis et al. further discloses that the methods and bisphosphonate compositions therein also comprise a histamine H2 receptor blocker (H2-antagoinsts), e.g., cimetidine, famotidin, and nizatidine, which are the instant preferred anti-ulcer agents, in order to minimize adverse gastrointestinal effects produced by a bisphosphonate (see col.13 lines 21-46).

Daifotis et al. does not expressly disclose that the total weigh of the solid compositions of the prior art is about 4.3 to about 6 grams such as 4.3 or 5 grams. Daifotis et al. does not expressly disclose that the acid component is about 51-52 % by weight of solid compositions of the prior art. Daifotis et al. does not expressly disclose the pH range claimed herein.

It would have been obvious to a person of ordinary skill in the art at the time the invention was made to determine or optimize the total weigh of the solid compositions of the prior art to 4.3 to about 6 grams, and the acid component to about 51-52 % by weight of solid compositions.

One having ordinary skill in the art at the time the invention was made would have been motivated to determine or optimize the total weigh of the solid compositions of the prior art to 4.3 to about 6 grams, since determining or optimizing the known amounts of bisphosphonate, solubilizing agents such as polyvivylpyrrolidone, coloring agents, and sweeteners in a pharmaceutical composition, and the determination or optimization of amounts of a known acid compound to be used to adjust the known pH of the buffering composition based on the prior art teachings, are considered well within conventional skills in pharmaceutical science, involving merely routine skill in the art.

Moreover, after administering of the liquid composition of Example 8 in Daifotis et al., the pH of the mammal's stomach would be inherently raised to about the claimed range since the citric acid solution is a known buffered solution which would mediate the pH in the mammal's stomach for a period of time.

It has been held that it is within the skill in the art to select optimal parameters, such as amounts of ingredients, in a composition in order to achieve a beneficial effect. See *In re Boesch*, 205 USPQ 215 (CCPA 1980).

Thus the claimed invention as a whole is clearly prima facie obvious over the teachings of the prior art.

Response to Argument

Applicant's arguments with the formulations' data in the table at page 7 filed September 23, 2004 and the declarations of Marshall A. Hayward, Ph.D. (not inventor) and Till Rohrich, Ph.D., submitted December 16, 2003 under 37 CFR 1.132 have been fully considered but are ineffective to overcome the 103(a) rejections herein as to nonobviousness or unexpected results for the method herein over the prior art, as further discussed below.

These arguments are believed to be adequately addressed by the obvious rejections presented above.

Additionally, Applicant asserts in the arguments and the declarations of Marshall A. Hayward and Till Rohrich that the pH value herein, 4.5 to about 5.5, is critical because the pH helps the stomach to rapidly eject the effervescent solution. Note that both Katdare and Daifotis et al. (5,994,329) have provided factual evidences that their bisphosphonate compositions comprising the same ingredients in the same or substantially similar amounts with the pH therein, either within or very close to the claimed range, are capable of minimizing the potential for adverse gastrointestinal effects. Thus, the patents cited have provided the same or substantially similar solution for the same problem as instantly claimed.

It must be recognized that any judgment on obviousness takes into account knowledge which was generally available and within the level of ordinary skill at the time the claimed invention was made. Knowledge of those skilled in art and nature of problem solved provided motivation and made obvious a combination of elements --

Princeton Biochemicals, Inc. v. Beckman Coulter, Inc. 04-1493 -- On June 9, 2005, recently the Federal Circuit upheld a finding of obviousness of Princeton's capillary electrophoresis device, used to separate proteins and other matter. This court upheld that motivation to combine the elements came from the knowledge of those skilled in the art and the nature of the problem solved by the invention.

In this case, as discussed above, the prior art patents have clearly provide the knowledge of those skilled in the art and the nature of the problem solved by the invention. Therefore, motivation to make the present invention based on the teachings of the prior art cited herein is seen. The claimed invention is clearly obvious in view of the prior art.

In view of the rejections to the pending claims set forth above, no claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Examiner Jiang, whose telephone number is (571)272-0627. The examiner can normally be reached on Monday-Friday from 9:00 to 5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Sreenivasan Padmanabhan, Ph.D., can be reached on (571)272-0629. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

S. Anna Jiang, Ph.D.
Primary Examiner
Art Unit 1617
July 18, 2005